[0081] Alternatively, components attached to beads and colloids can be pools of species.

[0082] The magnetic selection/dilution process described above will surely simplify analysis and enhance the accuracy of the experiment. However, it is not absolutely necessary in that the addition of DNA hybrid solutions alone will elucidate the identity of interacting pairs.

[0083] The signaling mechanism attached to the colloids need not be electronic or limited to the colloid. For example, the red color that the colloids impart when they agglomerate onto a surface can serve as the indicator that a species on a bead has interacted with a species on a colloid. In this case, the bead need not be magnetic. Alternatively, a fluorescent moiety can be attached to the colloids. Following an incubation period, the beads (magnetic or not) can be concentrated or pelleted so that the solution containing non-interacting colloids can be removed. Fluorescent beads are then separated from non-interacting beads and analyzed to reveal the identity of the interacting partners.

[0084] Although in the description above, "proteins" from a cDNA library are attached to the beads and colloids, the invention anticipates the attachment of a wide variety of putatively interacting species to the particles. These species may include, but are not limited to, chemical compounds, precursors of chemical compounds, reactive groups, protein complexes, nucleic acid-protein complexes, spores, cells, nucleic acids, peptides and drug candidates. These species can be attached to the colloids and beads via affinity tag interaction, non-specific binding, specific binding, or via covalent chemical coupling.

[0085] Additionally, the identifying tag attached to magnetic beads and colloids need not be nucleic acid based. Bead-colloid complexes can be separately released from the electrode pad and diverted to separate locations where the tags on the beads are deciphered. Identifying tags can include, but are not limited to, nucleic acid tags, radio frequency tags, fluorescent tags, fluorescence associated with a particle and chemical tags.

[0086] Various methods of the invention can be used to identify interaction motifs, rather than discrete binding partners. For this particular application, a first heterologous population of proteins is attached to a set of magnetic beads, and a second heterologous population of proteins is attached to a set colloids; each particle presents a single species. Following the magnetic selection-dilution process described herein, bead-colloid complexes are subjected to pool sequencing techniques to identify interaction motifs. Individual colloid-decorated beads are isolated. Each magnetic bead thereby presents a single species that is bound by a heterologous population of colloid-attached molecules. Interacting molecules are released from their particle supports by competitive inhibition of the affinity tag interaction. Interacting complexes are subjected to general enzymatic digestion by, for example, trypsin; interacting regions are protected from digestion. Complexes then are digested with N-terminal peptidase, which digests from the N-terminus to the point at which the interaction region or motif begins. After digestion, the interacting molecules are released from each other via acid elution. The mixture is then subjected to pool sequencing techniques, which typically involve Edman micro sequencing. The result of pool sequencing is that wherever there is a consensus motif, the identity of those amino acids is clear, while other regions appear as noise.

[0087] HPLC and similar techniques can be used to separate interacting species prior to sequencing analysis.

[0088] Alternatively, after colloid-decorated beads have been isolated, a first colloid-attached species can be released from their supports, via competitive inhibition of the affinity tag-colloid interaction, while a second set of proteins are allowed to remain bound to the beads. This can be accomplished by either having proteins bound to the beads via a different affinity tag interaction or by covalently coupling species to the beads. Enzymatic digestion then is performed while protein pairs remained bound to the beads. This procedure preferentially digests the first protein that is not directly attached to the bead, while protecting the second bead-attached species. Digestion products can be easily removed by concentrating the beads discarding the supernatant. The first species can then be eluted from its binding partner by acid elution or similar techniques. The supernatant, which contains the digested first species is then subjected to pool sequencing techniques to elucidate a consensus binding motif(s). The second species can be released from the bead and subjected to pool sequencing. Alternatively, the procedure can be repeated with the first species, or a consensus sequence derived from the first species, attached to the bead and the second species attached to the colloids.

[0089] Methods of the invention can be performed with: a single species presented on the colloids and many species attached to beads; many species attached to colloids and many species attached to beads; or many species attached to colloids and a single species attached to beads. Additionally, a mixed population of particles, each presenting a single distinct species can be used or a mixed population of particles presenting mixed species. In another aspect of the invention, magnetic beads that have been coated with a layer of interacting colloids are electromagnetically selected on the basis of differential mass. Alternatively, colloids can be modified to present not only a putative binding partner, but also a moiety that will impart differential electromagnetic properties when complexed with a magnetic bead(s). Magnetic beads decorated with these colloids can then be selected, separated and analyzed to reveal the identity of the particle-immobilized interacting partners.

[0090] In yet another aspect of the invention, the bead need not be magnetic. Colloid-bead complexes can be separated from unbound colloids by sedimentation, centrifugation or by physically removing beads that become decorated with colloids that may or may not present auxiliary signaling elements.

[0091] Similarly, particles that present putative binding partners with or without auxiliary signaling elements need not be colloidal. For example, molecules can be directly incorporated into liposomes along signaling moieties, such as ferrocene derivatives coupled to lipids. Alternatively, molecules can be attached, via affinity tag interaction, to liposomes that also incorporate binding partners for affinity tags.

[0092] Methods of the invention can be performed using a heterologous population of colloids that each present a single species or colloids that present more than one species. Species that can be attached to particles, as described herein, include but are not limited to proteins, domains or fragments of proteins, such as kringle domains, small molecules, natural products, and drugs.